

# Osteonecrosis of the jaws in patients with a history of receiving bisphosphonate therapy

Strategies for prevention and early recognition

MAICO D. MELO, D.M.D.; GEORGE OBEID, D.D.S.

**B**isphosphonates, inhibitors of osteoclasts, have been used for many years in the treatment of resorptive bone diseases including osteoporosis, Paget's disease and hypercalcemia related to malignancy. However, bisphosphonates also have been shown to inhibit angiogenesis and induce apoptosis in tumor cells.<sup>1-6</sup> These features have made bisphosphonates useful in the treatment of metastatic bone disease.

**Clinicians need to be aware of bisphosphonate-related osteonecrosis because they are in a position to recognize and possibly prevent this complication of cancer treatment.**

## BACKGROUND

Several clinical trials have demonstrated the beneficial effects of bisphosphonates in reducing skeletal complications such as pain and pathological fracture in patients with bone metastases.<sup>7-10</sup> On the basis of the results of these trials, oncologists commonly prescribe bisphosphonates to treat bone lesions of multiple myeloma and metastatic bone lesions in patients with breast and prostate cancer.<sup>11,12</sup> Recently,

the indications for bisphosphonate treatment were expanded to include osteolytic lesions from any solid tumor, which has resulted in a marked increase in the use of bisphosphonates.<sup>13</sup>

**Background.** Bisphosphonates, inhibitors of osteoclasts, have been shown to alleviate many of the devastating consequences associated with metastatic bone disease. However, recent reports have shown that bisphosphonates may cause osteonecrosis of the jaws. Since the publication of these initial reports, the authors have treated several patients with osteonecrosis of the jaws who had a history of receiving bisphosphonate therapy.

**Methods.** The authors reviewed the medical records of patients who visited their clinic between September 2003 and December 2004 and who had osteonecrosis of the jaws and a history of having received bisphosphonate therapy but no irradiation to the head and neck.

**Results.** Eleven patients (four female and seven male) with a mean age of 69 years were included in this report. They had received bisphosphonate therapy for a mean duration of 34 months. Radiographic data showed loss of bone density at sites of osteonecrosis, and histologic examination demonstrated necrosis of bone without evidence of metastases.

## Conclusions and Clinical

**Implications.** Further research is required for better understanding of the role of bisphosphonates in the development of osteonecrosis of the jaws. Until more is known, the authors recommend that measures be taken to prevent osteonecrosis in those at risk, including identifying patients with a history of having received bisphosphonate therapy before they undergo dental surgery. To help identify such patients, the authors propose the use of a screening questionnaire. When feasible, physicians should consult with their patients' general dentists or oral surgeons before patients begin bisphosphonate therapy.

**Key Words.** Bisphosphonates; osteonecrosis; bone disease; malignancy.

TESTIMONIO DE AUTENTICIDAD

YO, CARMEN ERMITA MARTINEZ AYALA conocida por EREMITA MARTINEZ AYALA, mayor de edad, viuda, ama de casa y vecina del municipio de Cabo Rojo, Puerto Rico, bajo juramento declaro lo siguiente:

1. Que mi nombre y demás circunstancias personales son las antes expresadas.

2. Que a pesar de que mi Certificado de Nacimiento aparezco inscrita con el nombre de Carmen Ermita Martínez Ayala siempre he usado el nombre de Eremita Martínez Ayala en asuntos y documentos oficiales.

3. Que entre los documentos en que aparezco usando el nombre de Eremita Martínez Ayala se encuentran:

- a) Tarjeta de Seguro Social número 581-03-8480.
- b) Certificado de Matrimonio.
- c) Certificados de Nacimiento de mis hijos.

4. Que deseo dejar establecido por medio de este documento que Carmen Ermita Martínez Ayala y Eremita Martínez Ayala son una y la misma persona y los nombres por los cuales soy conocida.

5. Que hago esta declaración de buena fe sin ánimo de adquirir derechos que no me correspondan, ni de burlar ley alguna.

Y PARA QUE ASI CONSTE, juro y signo la presente en Cabo Rojo, Puerto Rico, a 14 de enero de 1993.

*Carmen Ermita Martínez Ayala GP.*  
CARMEN ERMITA MARTINEZ AYALA conocida  
por EREMITA MARTINEZ AYALA

*Eremita Martínez Ayala*

AFFIDAVIT NUM. 5872

YO, GILBERTO ACOSTA AYALA, Notario Público con residencia oficial en Cabo Rojo, Puerto Rico, DOY FE:

Que considero legítima la firma que antecede de doña Carmen Ermita Martínez Ayala conocida por Eremita Martínez Ayala, mayor de edad, viuda, ama de casa y vecina del municipio de Cabo Rojo, Puerto Rico, por haberse identificado debidamente la firmante por los medios establecidos en ley y por haber estampado su firma en mi presencia, hoy 14 de enero de 1993.

*Gilberto Acosta Ayala*  
NOTARIO PÚBLICO



*Le envío copia ya  
que ella no utiliza  
el Carmen ella firma  
Eremita Martínez Ayala*

#20195 — Medical Arts Press 1-800-328-2179

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12/4/98

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- Stepper 60g + 16g

- Tissue sample 16g + 16g

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Handwritten notes in the left margin, possibly indicating a date or reference number.

name (S) - no name, no names in return & press  
 Red. friends, separate, no dates, no name, no regular  
 then still good

Got up - he is here (has photo)

A. Diction

C - months 10 y i in 10 months

- foreman say only

- X called up & d i will

- Oswald. ult. 8/15/60, 10/15/60, 11/15/60

P

08/17/60

12/1/60

114

the object R & L

ult. 10/10/60 50-60

R & L 4-6

Best - loaded

Sp. Septor 21 dail x 7 dail

Refuter ult.

Chasing  
 (see - 11)

Q

09/10/60

14/1/70

1136

the R & L ult. 1/1/70 to 1/1/70 to 1/1/70

O. Brown al

(see - 11)

A ult - up

P -

Q

12/1/60

110/20

P 56

1586

the R & L ult. 1/1/70 to 1/1/70 to 1/1/70

a last time

who R & L a press 1/1/70. no letters from

O. Brown - C

(see - 11)

Got up - no name, press photo

A. Diction

A. Cien - Complex & process

P. 20/1/70 21/1/70 x 7 dail (see - 11) 50, 10/1/70

Cyanide 100 in 100

X-ray 1/1/70 i in



Inf. See name Rogier

P.

04-09-01

11/0/80

160

1076

2. (H) there 2-3 cases. The first is a person called  
who belongs to the neighborhood and was a friend of the person.  
There, quite, no line, no cases. De noche  
wele, the cases go to the window. He saw something  
in the house and went to the window.

0. Diego - house

Cocina e

Cher - Co.

Abel, friend, superior, no idea, no man,

friend. A.

Today - the colony

1. Diego is a friend of the person

1. Cocodrilo. He was the first to see the person.

- White dog and a red dog, white dog and

- Lycopodium 2.5m and a 1.5m

- Xanthox 1.4m

- Out of 100,000 and 100,000

- By Don name Rogier CPC Clinic

- Out of 100,000

P

05-10-01

12/1/81

1106

PS the first to see. He is a friend of the person.  
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He is a friend of the person and he is a friend of the person.

0. Diego - house

Cher - Co.

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A. He is a friend of the person.

1. Out of 100,000

Xanthox 1.4m

Che friend of the person

P



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01/04/09

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1126

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01-09-93

100/20

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9

07/11/03

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John & John.

Cheryl, who was up to 100-100 2000 H&B 9. AC  
TID

Q

07/10/03

100/60

Piz

1136

2.18 the first to John. You are a former re George  
to make sure

0. Dredge fragments

Green. No objection

Green

Cheryl

Red. Please, depend on details. (Parker) make

foot reg - he done. (W. make

A. FBI 138 2000 186 H&B 9. AC 7.37.  
CUT 243 100 to 1000

Page 217

1 - 100/60 1000 1000 to 1000

- 2.18 20, 1000

- 1000/1000

- CUT 2000 FBI 2000, CUT 100-100 Page  
01603.

Q

11/04/03

100/60

1112

2.18 the first to John. 1000 1000

0. 1000  
1000 - 1000

A. FBI 119 2000 140

CUT 204 100 100 100 Page 140

0. - CUT 1000

- 1000/1000

- CUT 2000 FBI 2000 H&B 9. AC CUT 100-1000  
CUT

02-18-04

116/88 Pco

111

d. (8) The first de lib. to route bin  
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1. 13.8 FAX 155  
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Cur 22

138 48

Tip 157

143

1. (8) The first de lib. to route bin

Foreign 13.8

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Met 13.8 13.8

Met 13.8 13.8

Met 13.8 13.8

Met 13.8 13.8

4

04/11/04

Met 13.8 13.8

04/11/04

120/60

Pco

109

d. (8) The first de lib. to route bin  
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Cur 237

138 53

Tip 127

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143

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Met 13.8 13.8

- *Lipin 20, 100*  
 - *Lipin 20, 100*  
 - *FB3 117*

09/09/04

140/85

109

2. *the pro de facto: the court says*

O. *the pro de facto: the court says*

*the pro de facto: the court says*

A. *FB3 117*  
*100 137*

P. *Lipin 20, 100*  
*the pro de facto: the court says*

*the pro de facto: the court says*

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*FB3 117*  
*100 137*  
*the pro de facto: the court says*

11/09/04

140/85

106

105

2. *the pro de facto: the court says*

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*the pro de facto: the court says*

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*100 137*  
*the pro de facto: the court says*

P. *Lipin 20, 100*  
*the pro de facto: the court says*

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*FB3 117*  
*100 137*  
*the pro de facto: the court says*



01-20-05

120/A

110'K

2.8 the Re de hel. to punto 52

0. Curc  
Green Cer.

A. FRS 127

COT 149

AST-17

WASP 194

WOL 41

Pig 151

AOT 34

WOL 82

1. Glipiride 2.07 rd

dipiride 0.07 rd

Virus 1.07 rd

Lip. to 2.07 rd

Ciba diel 0.07 rd CMB Lpox 0.07 rd

107. Mc 0.07 rd

C.

04/29/07

120/A

168

110'K

2.8 the Re de hel. to punto 52

0. Curc  
Green Cer.

A. FRS 120

COT 171

WASP 135

WOL 39

Pig 184

107. 6.87

WOL 96

1. Glipiride 2.07 rd

dipiride 0.07 rd

Virus 1.07 rd

Ciba &amp; Cigito FRS WOL 107. Mc 0

0.07 rd

08/10/07

120/A

170

110

2.8 the Re de hel. to punto 52

to punto 52

0. Curc  
Green Cer.

Ciba. no paper &amp; paper

0.07 rd - no paper (no paper)

2000	20
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APR 2000 x 2

Chloride of mercury

Wipke-Landau 07 - d

June 14 1911

2

12/24 (or

Après que j'ai vu ce compte de dépenses  
de la part de nos amis, j'ai fait  
de même.

0. CDR - 0

John. Jones

l'ien - Je donne - Je prends de la photo de  
les x's . (les points) .

1. Jules phère de la pizza  
2. 8 Days Both feet in the + de.


L. J. Jones

CS-mi dmi 21880 100% 7-Me 2yr 16.

12/27/05

1-8 mgie - <i>Arundinaria</i> 9-12 mgie - <i>Arundinaria</i>	13-16 mgie - <i>Arundinaria</i> 17-20 mgie - <i>Arundinaria</i>	21-24 mgie - <i>Arundinaria</i> 25-28 mgie - <i>Arundinaria</i>	29-32 mgie - <i>Arundinaria</i> 33-36 mgie - <i>Arundinaria</i>	37-40 mgie - <i>Arundinaria</i> 41-44 mgie - <i>Arundinaria</i>	45-48 mgie - <i>Arundinaria</i> 49-52 mgie - <i>Arundinaria</i>	53-56 mgie - <i>Arundinaria</i> 57-60 mgie - <i>Arundinaria</i>	61-64 mgie - <i>Arundinaria</i> 65-68 mgie - <i>Arundinaria</i>	69-72 mgie - <i>Arundinaria</i> 73-76 mgie - <i>Arundinaria</i>	77-80 mgie - <i>Arundinaria</i> 81-84 mgie - <i>Arundinaria</i>	85-88 mgie - <i>Arundinaria</i> 89-92 mgie - <i>Arundinaria</i>	93-96 mgie - <i>Arundinaria</i> 97-100 mgie - <i>Arundinaria</i>
-----------------------------------------------------------------	--------------------------------------------------------------------	--------------------------------------------------------------------	--------------------------------------------------------------------	--------------------------------------------------------------------	--------------------------------------------------------------------	--------------------------------------------------------------------	--------------------------------------------------------------------	--------------------------------------------------------------------	--------------------------------------------------------------------	--------------------------------------------------------------------	---------------------------------------------------------------------

de lo inserto al folio 65 y le pinto por donde  
i Newby + Salmeron 17.





- Side note As before Ad. A/B
- Ruff so, bare
- 2 legs (B) head perfect.

Gripes - de XL 20y old  
Dipicid and he 20y old

28/2/6

130/80

168

[illegible]

0.1 Worms & Pucc. Ques.

mejor. (entre ellos de la mano)

Mel. ~~Frank Doyle~~ <sup>Frank Doyle</sup> ~~has been~~ <sup>has been</sup> ~~set up~~ <sup>set up</sup> - ~~Western~~ <sup>Western</sup>  
 & ~~Doyle~~ <sup>Doyle</sup> ~~has been~~ <sup>has been</sup> ~~set up~~ <sup>set up</sup> - ~~Western~~ <sup>Western</sup>

A. K. Gupta (10) Hindi - 05

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Ans to qy.

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1. - by reading

- Right Hemisphere

- Ruler 600 - 600

~ FRX 2400 11hp % AL-

Michigan

Lipid Rafts  
abundant - concentrated

- 15 Sept

~~James in 14.~~

## CONTINUATION SHEET

11/04/06

120/60 P60

102

d. 12 The (de la) lab. p. (de la) neg. 12.

O. Con - c

(the) Con.

first of - no exam. (the) p. 12

A. (the) 216

FRS 116

120 3 9

Dy - 102

2000 118

120 141

1000 (the) 6.4).

PWS 13

Heinrich 4.2

cont 0.7

WBL 8,600

120 13.7

(the) 302,000

O.

Glennide XL 257 + d.

D. (the) 100, 100

D. (the) 100, 100

C. (the) 100, 100

Lupin (the) 100, 100

C.

11/05/07

120/60 P60

103

d. 12 The (de la) lab. p. (de la) neg. 12.

O. Con - c

(the) Con.

first of - no exam. (the) p. 12

A. OB - 12

FRS 106

(the) 197

2000 110

120 36

1000 (the) 6.1).

120 131

Heinrich 0.844.

Tij 139

Cont 8.9

PWS 10

cont 0.7

O.

Glennide XL 257 + d.

D. (the) 100, 100

D. (the) 100, 100

C. (the) 100, 100

Lupin (the) 100, 100

C.



Crth 3 was - - FFA 2080 10/1/Alc.

d. mid 1970s LBC

lp

Nombre del paciente

Remita María Galt # 1314

Fecha

Diente

Sup.

Notas de tratamiento

11/20/00 (3 MO) Condite; no anestesia usada  
Postscure fibron cementado con  
calibron; PJ

11/23/05  
Para x-rays; 1 PA #5  
Paciente tiene distadurea max y el área  
de la extracción #5 la cual fue  
aplicada por otro dentista ism  
inflamada y tiene mucha molestia  
La extracción la aplicaron hace  
6 meses aproximadamente y desde  
entonces ha estado sangrando  
por tiempos y no ha sanado bien

Se le informó a la paciente que tenía  
que hacer la distadurea para evitar posible  
trauma

Examen Perioral; prótesis PJ  
Inclusión 300m; 12 bñr.

12/5/05  
1 PA x-ray oclusal del área #5; la  
cual continúa inflamada se ve  
área de extracción que no ha sanado  
completamente; la cicatrización después  
de todo este tiempo no se ve bien

Refiere al Maridafanal Dr Oscar Moniz para  
evitar área; no se ve muy atendida  
pero paciente tiene historial de cáncer oral  
hace 3 años y se refiere para evitarse.

1/23/06  
Paciente no fue a continuación  
con Maridafanal, cuando se refirió  
y en esos momentos me dice "me está  
dolorando un rayo"

1/23/06 Maridafanal se dieron áreas  
con mucha infección y solo pedazo de  
hueso aproximadamente; se envió a patología

Nombre del paciente Fernita María Ayala #1314

Fecha	Diente	Sup.	Notas de tratamiento
			Con el Dr. J. J. Wescovich en Haysburg. En el reportaje se describe que puede haber Quirón de cáncer de seno y que el área aparentemente como un cáncer de seno. Se le recetó en el seno 30mg 1/2/2h
2/2/06			Cita de seguimiento. Paciente está bien. WNL en el recto. Punguiderm (en la gran área).
2/3/06			Dr. Wescovich llamó para aclarar dudas sobre paciente y me preguntó si se le había biopsiado y si se le había hecho si se le exploró todo por la zona.
			Patología a unete de cancer (ver copia en el expediente)
2/7/06			Paciente me informó se esforzó para con Dr. Juan Martínez y la idea de actuar y se le entregó copia de la patología

PATOLOGIA ORAL Y MAXILOFACIAL DEL OESTE  
P.O. BOX 8053 MARINA STA.  
MAYAGUEZ, PR 00681  
TELEFONO (787) 891-9155

**PATHOLOGY REPORT**

DATE: FEBUARY 02, 2006  
PATIENT: CARMEN MARTINEZ  
REFERRING DOCTOR: ROSA GARCIA

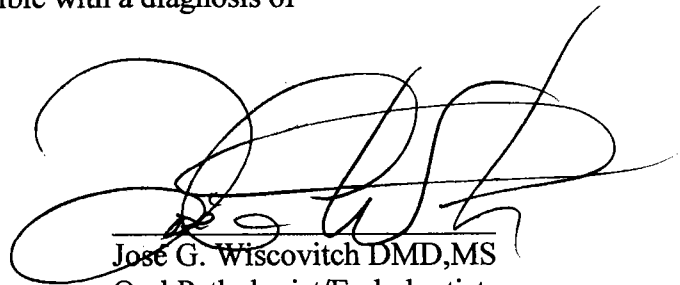
LAB. NO.: OP-016-06  
AGE: Y/O SEX: F

**HISTORY:** Older aged female with a history of an extraction done by another general practitioner five or six months ago still presents non-healing socuet with seropurulent exudate. The extraction was related to a tooth #4 in close proximity with the maxillary sinus. Past medical history includes breast cancer and at present patient is taking Fosamax every week for the last five years. Second clinician sees patient for evaluation and confirms a none-healing extraction area at the right maxilla. Clinician debrided the area and obtained a conspicuous amount of a purulent exudate with a fibrinous coagulum. Clinician submitted specimen for histopathologic examination with no provisional clinical diagnosis.

**MICROSCOPIC:** Histologic examination reveals multiple sections of an exuberant granulation tissue with large areas of hemorrhage lined in some areas by a hyperplastic nonkeratinized stratified epithelium. This tissue has a diffuse and intense admixture of chronic and acute inflammatory cells. In some areas, aggregates of polys in a purulent/edematous background are evident. In addition, some portions of the specimen contains amorphous basophilic colonies of microorganisms. Nonviable bone spicules are evident throughout the specimen.

**DIAGNOSIS:** Hyperplastic subacutly inflamed granulation tissue with focal abscess formation, basophilic bacterial colonies and nonviable bone fragments, extraction area of tooth #4.

**COMMENTS:** The histologic features when combined with the radiographic appearance and the present and past medical history is compatible with a diagnosis of osteochemonecrosis.

  
Jose G. Wiscovitch DMD,MS  
Oral Pathologist/Endodontist